Sequencing Quadruple Therapy for Heart Failure with Reduced Ejection Fraction: Does It Really Matter?

Jiun-Ruey Hu, MD, MPH[a], Alexandra N. Schwann, MD[b], Jia Wei Tan, MD[c], Abdulelah Nuqali, MBBS[a], Ralph J. Riello, PharmD[a], Michael H. Beasley, MD[a,*]

KEYWORDS

• Guideline-directed medical therapy • Heart failure with reduced ejection fraction • Tolerability • Sequence • Renin–angiotensin aldosterone system inhibitors • Beta blockers • Mineralocorticoid receptor antagonists • Sodium–glucose cotransporter 2 inhibitors

KEY POINTS

- The conventional sequence of guideline-directed medical therapy (GDMT) initiation (renin–angiotensin system inhibitors- > beta blockers- > mineralocorticoid receptor antagonists [MRAs]- > sodium–glucose cotransporter 2 inhibitors [SGLT2i]) assumes that the effectiveness and tolerability of GDMT agents mirror the order in which they were historically developed, which is not true.
- Flexible GDMT sequencing should be permitted in special populations, such as patients with low blood pressure, low heart rate, chronic kidney disease, or atrial fibrillation.
- The initiation of certain GDMT medications may enable or increase tolerance of other GDMT medications (eg, SGLT2i reducing the risk of hyperkalemia and worsening renal function, thus enabling the use of angiotensin and neprilysin inhibitors and MRA), so sequencing strategy plays a role in at-risk populations.
- The achievement of partial doses of all four pillars of GDMT is better than achievement of full doses of incomplete (< four) pillars of GDMT.
- Deferring initiation of GDMT to the outpatient setting carries a greater than 75% chance that it will not be started within the next year due to therapeutic inertia and the "stickiness" of medications carried over from the inpatient setting.

INTRODUCTION

Although the development of novel pharmacologic treatments, interventional techniques, and advanced therapies for patients with heart failure (HF) has ushered in a mini-renaissance for the management of after decades of stagnancy, the implementation of guideline-directed medical therapy (GDMT) remains the bedrock of HF treatment. The primary goal of clinicians caring for patients with HF with reduced ejection fraction (HFrEF) is to prolong high-quality life with the fewest invasive interventions possible. This is the promise of GDMT. Patients with new onset HF

[a] Clinical and Translational Research Accelerator, Yale School of Medicine, New Haven, CT 06520, USA; [b] Department of Internal Medicine, Yale New Haven Hospital, P.O. Box 208030, New Haven, CT, 06520-8030, USA; [c] Division of Nephrology, Stanford University School of Medicine, 780 Welch Road, Palo Alto, CA 94304, USA
* Corresponding author.
E-mail address: michael.beasley@yale.edu
Twitter: @ruey_hu (J.-R.H.); @aschwann212 (A.N.S.); @jiiiiawei (J.W.T.); @AbdulelahNuqali (A.N.); @ralphadelta (R.J.R.); @MHBeasleyMD (M.H.B.)

Cardiol Clin 41 (2023) 511–524
https://doi.org/10.1016/j.ccl.2023.06.007
0733-8651/23/© 2023 Elsevier Inc. All rights reserved.

SHOUT
SHARE
IT

may initially present in cardiogenic shock. Yet after hemodynamic stabilization, initiation of GDMT, close monitoring, and outpatient follow-up, it is not uncommon for systolic function to markedly improve, allowing the patient to return to normal life. This return to normalcy can persist for many years, as long as disease-modifying therapies are continued.[1] How should clinicians implement these life-saving treatments for patients with HFrEF? Does the sequence in which GDMT matter as long as all recommended classes of therapy are eventually prescribed?

In practice, there may be as many methods of initiating and titrating as there are cardiologists. The latest American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines strongly recommend early initiation of all four pillars of GDMT: (1) renin–angiotensin system inhibitors (RAASis) including angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor blockers (ARBs)/angiotensin and neprilysin inhibitors (ARNis), (2) beta blockers (BBs), (3) mineralocorticoid receptor antagonists (MRAs), and (4) sodium–glucose cotransporter 2 inhibitors (SGLT2is) for patients with HFrEF.[2] Further details can be found at www.GDMT.org.[3] We recognize the importance of broad implementation of all four classes of GDMT as soon as possible, followed by rapid titration (**Table 1**) to target or maximally tolerated dosing. The purpose of this review is to highlight certain clinical scenarios in which the order of GDMT initiation during an acute HF (AHF) hospitalization can play a significant role.

TOLERABILITY, SAFETY, AND EFFICACY

Inpatient initiation and intensive up-titration of GDMT for patients hospitalized with AHF was examined in the STRONG-HF trial.[4] It compared a high-intensity intervention involving the rapid up-titration of GDMT versus usual care among patients with an admission for AHF. Intensive GDMT implementation and close follow-up was not only safe but also reduced the risk of 180-day all-cause mortality or HF readmission by 34%, with an adjusted risk difference of 8.1% ($P = .0021$) and adjusted risk ratio of 0.66.[4] The study was terminated early due to a larger than expected risk reduction of the primary endpoint in the high-intensity care group. Of note, patients were enrolled in this trial before the approval of SGLT2i for HFrEF. Thus, the GDMT in this study included ACEi/ARB/ARNi, BB, and MRA.

RENIN–ANGIOTENSIN SYSTEM INHIBITORS

Traditionally, patients with HFrEF were prescribed an ACEi or ARB as foundational disease-modifying therapy. Given the superior morbidity and mortality reduction seen with ARNi, sacubitril–valsartan is now the preferred RAASi—even in *de novo* HFrEF. It is also strongly recommended to actively transition stable patients on an ACEi or ARB to an ARNI as soon as possible.[5] Inpatient initiation of ARNI in patients with *de novo* HFrEF is supported by the PIONEER-HF trial.[6] In this study, 881 patients with HFrEF hospitalized for AHF were randomized to sacubitril–valsartan or enalapril after hemodynamic stabilization, defined as the absence of intravenous (IV) inotropic medication within 24 hours and no IV vasodilators, diuretic dose escalation, or systolic blood pressure of less than 100 mm Hg in the previous 6 hours. Patients initiated on sacubitril–valsartan had significantly lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) serum concentrations at 8 weeks (−46.7% vs −25.3%, $P<.001$). Of note, the rates of worsening renal function (WRF), hyperkalemia, and symptomatic hypotension were similar between the treatment groups, supporting the safety and tolerability of in-hospital ARNi initiation. This study also highlights the potential benefit of sacubitril–valsartan in an expansive cohort of American patients, including decompensated patients with a history of HF and those with newly diagnosed HF.

BETA BLOCKERS

In patients hospitalized with AHF, the initiation of BB therapy is often delayed due to concerns that sympathetic nervous system antagonism may exacerbate an acute decompensation—particularly if incorporated before decongestion and hemodynamic stability. It is important for providers to recognize low-output states and cardiogenic shock early as BB should indeed be avoided during this period. In the appropriate hospitalized HF population, however, BB treatment before discharge is associated with improved clinical outcomes. IMPACT-HF randomized 375 patients admitted with AHF to either in-hospital carvedilol introduction before discharge or delayed carvedilol initiation at least 2 weeks after discharge during routine outpatient follow-up. Patients treated with carvedilol in the acute care setting—approximately 60 hours into hospital admission—had significantly better medication adherence (91.2% vs 73.4%, $P<.0001$) and a greater likelihood of reaching target dosing within 60 days. Inpatient initiation of carvedilol did not seem to confer any increased risk for adverse events including similar length of stay, rates of worsening HF, hypotension, or bradycardia.[7] BBs are commonly reported to have adverse effects, including dizziness, bradycardia, and low blood pressure, and these may

Table 1
Examples of studies that involved initiation or up-titration of guideline-directed medical therapy in patients hospitalized with heart failure

Class	Target Dose	Adverse Effects	Monitoring Parameters	NNT for All-Cause Mortality[2] (Standardized to 36 mo)
β-Blocker	• Bisoprolol 10 mg daily • Carvedilol 25 mg BID, if < 85kg • Carvedilol 50 mg BID, if ≥ 85 kg • Metoprolol Succinate 200 mg daily	• Bradycardia • Dizziness • Fatigue • Hypotension	• Blood pressure • Heart rate	9
ACEi	• Captopril 50 mg 3× daily • Enalapril 10–20 mg BID • Lisinopril 20–40 mg daily • Ramipril 10 mg daily • Trandolapril 4 mg daily	• Acute kidney injury • Angioedema • Cough • Hyperkalemia • Hypotension	• Blood pressure • Potassium • Serum creatinine	26
ARB	• Candesartan 32 mg daily • Losartan 150 mg daily • Valsartan 160 mg BID	• Acute kidney injury • Hyperkalemia • Hypotension	• Blood pressure • Potassium • Serum creatinine	26
ARNi	Sacubitril–valsartan 97–103 mg BID	• Acute kidney injury • Angioedema • Cough • Hyperkalemia • Hypotension	• Blood pressure • Potassium • NT-proBNP • Serum creatinine	27
MRA	• Eplerenone 50 mg daily • Spironolactone 50 mg daily	• Hyperkalemia • Gynecomastia (S > E)	• Blood pressure • Potassium • Serum creatinine	6
SGLT2i	• Dapagliflozin 10 mg daily • Empagliflozin 10 mg daily	• Acute kidney injury • Dyslipidemia • Genital mycotic infection • Hypoglycemia • Ketoacidosis • Urinary tract infection	• Glucose • Hemoglobin A1c • Serum creatinine • Volume status	22

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal proB-type natriuretic peptide; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

lead to intolerance and discontinuation with chronic treatment.[8] Given the significant mortality benefit in patients receiving all four classes of GDMT, clinicians can consider low dosing and slow up-titration of BB to better improve tolerability. It should be noted that although the practice of initiating metoprolol tartrate with transition to metoprolol succinate is prevalent in AHF, this is a practice likely carried over from acute myocardial infarction management and is not supported by clinical trial evidence in HFrEF.

MINERALOCORTICOID RECEPTOR ANTAGONISTS

Despite the immense magnitude of mortality benefit and long-standing affordability, MRA is the least frequently prescribed pillar of GDMT.[9] Concerns limiting prescriber uptake of MRA include the perceived risk of hyperkalemia or WRF.[10] The COACH trial found reduced 30-day mortality and rehospitalization rate in patients admitted with AHF who were discharged on spironolactone, with more notable benefit in higher risk patients, compared with patients not discharged on spironolactone (hazard ratio [HR] 0.362, $P = .027$).[11] The ATHENA-HF trial randomized MRA naive or low-dose MRA patients who presented with at least one sign or symptom of HF with concurrent elevation in NT-proBNP greater than 1000 pg/mL within 24 hours of admission to spironolactone or placebo. Although MRA treatment did not demonstrate improvement in the primary or secondary outcomes, high-dose spironolactone was shown to be well tolerated in the hospital setting without any increased risk of hyperkalemia or decreased renal function when compared with placebo.[12] To decrease the risk of hyperkalemia, the initiation of potassium binding resins and/or consideration of MRA dose reductions or alternate day dosing should be considered before discontinuation of therapy.[13,14] Hyperkalemia risk among MRAs may be related to differences in mineralocorticoid receptor selectivity and relative concentrations in cardiac versus renal tissues; there is some evidence to suggest that spironolactone may carry a higher risk of hyperkalemia, however, there has never been a direct comparison between the two drugs.[15] Eplerenone generally confers fewer adverse drug effects than spironolactone, most notably for gynecomastia and other sexual side effects which are known to be a reason for nonadherence among patients.[16] Initiation and continuation of MRA therapy can be challenging in certain patient populations, as its use is contraindicated in men with a serum creatinine greater than 2.5 mg/dL and women with a serum creatinine greater than 2mg/dL as well as all patients with an estimated glomerular filtration rate (eGFR) $\leq$ 30mL/min/1.73m.[2]

SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS

SGLT2i are the newest pillar of GDMT. Initially approved for the treatment of type 2 diabetes mellitus, the significant morbidity and mortality benefit of this class is noted to be independent of whether a patient is diabetic or not. Unlike other classes of GDMT, SGLT2i are the simplest to add to a patient's regimen given their tolerability and once daily dosing with no need for titration. The EMPULSE trial randomized 530 patients admitted for AHF to empagliflozin or placebo and found a reduced risk of all-cause mortality and HF events at 90 days in the patients randomized to empagliflozin. Patients in the empagliflozin arm were also found to have improvement in their HF symptoms.[17] A meta-analysis of the DAPA-HF and EMPEROR-Reduced trials noted that empagliflozin and dapagliflozin were associated with a reduction in all-cause death, cardiovascular death, and rate of HF hospitalization with improved renal outcomes.[18] The EMPA-RESPONSE-AHF randomized 80 diabetic and nondiabetic patients admitted with AHF to empagliflozin or placebo within 24 hours of admission. The initiation of empagliflozin was noted to improve diuresis with increased urinary output and had a significant decrease in the combined endpoint of in-hospital worsening HF, death, and hospital readmission within 60 days. The exact mechanism of benefit of this class remains debated but is thought to be related to the natriuresis promotion without associated RAAS activation and sympathetic tone. It is important to note that nondiabetic patients are not at an increased risk for hypoglycemic events. SGLT2i exert minimal to no effect on blood pressure but often with the initiation of this class providers must monitor volume status and consider a reduction in patients' diuretic doses.[19] The addition of this class is crucial, as SGLT2i have been found to enable tolerability when prescribed alongside other pillars of GDMT, decreasing risk of hyperkalemia and acute kidney injury (AKI).[19] SGLT2i do not increase patients' risk for urinary tract infections; however, genital mycotic infections have occurred more commonly with this class than placebo.[20]

GUIDELINE-DIRECTED MEDICAL THERAPY SEQUENCING IN SPECIAL POPULATIONS

Rationale for Flexible Sequencing

The conventional approach for GDMT initiation involves increasing each agent to target dosing

before the initiation of another agent, and doing so in the "order of discovery": RAASi - > BB - > MRA - > SGLT2i. However, the conventional approach assumes that the effectiveness and tolerability of the GDMT agents (**Table 2**) mirror the order in which they were historically developed, which is not true. In addition, the conventional approach neglects to recognize that the beneficial effect of each drug is additive and independent of prerequisite achievement of target doses of prior drugs. A rigid adherence to this approach will deprive or delay the achievement of full GDMT in certain patients. For instance, McMurray and Packer make a convincing case for the simultaneous initiation of SGLT2i and BB, as SGLT2i are very well-tolerated and do not require dose titration.[21] In the sections that follow, we describe strategies for flexible GDMT sequencing in special patient populations. These clinical phenotypes can be dynamic—patients may transition between different phenotypes over the course of their illness.

The initiation of all four pillars of GDMT takes priority over the optimization of an individual medication to target dosing.[22] GDMT initiated during an inpatient encounter are much more likely to "stick" as chronic outpatient medications. Deferring initiation of GDMT to the outpatient setting is associated with a greater than 75% chance that GDMT will not be started within the next year.[23]

Heart Failure with Reduced Ejection Fraction with Hypotension

It should be noted that low BP may be a reflection of progression of pump failure, overdiuresis, dehydration, ischemia, gastrointestinal bleeding, autonomic dysfunction, infection, or another unrelated pathologic process. In HFrEF patients who have persistent borderline hypotension after the treatment of reversible causes of acute hypotension, SGLT2i and MRA can be first considered, as these medications usually minimally affect blood pressure.

SGLT2i are "smart" diuretics that reduce plasma volume without the compensatory neurohumoral and renin–angiotensin-aldosterone system activation.[24] In DAPA-HF, the rate of discontinuation of dapagliflozin and placebo in patients with baseline SBP of less than 110 mm Hg was no different from that in patients with baseline SBP 110 to 120, SBP 120 to 130, and SBP $\geq$130.[25] In patients with baseline SBP less than 110 mm Hg, the between-treatment difference of dapagliflozin compared with placebo was -1.50 mm Hg at 2 weeks, -1.05 mm Hg at 2 months, and -0.68 mm Hg at 8 months.[25] In EMPULSE, the adjusted mean SBP change was +0.1 mm Hg in the empagliflozin group and +1.0 mm Hg in the placebo group at 3 months.[17,25,26]

Regarding MRA, pooled data from RALES and EMPHASIS-HF fascinatingly demonstrated an increase in SBP in those with low baseline SBP. At 1 month, patients with baseline SBP $\leq$ 105 mm Hg increased by 6.1 mm Hg in the MRA arm and 8.9 mm Hg in the placebo arm, with a between-treatment difference of 2.8 mm Hg. At 6 months, SBP further increased to 9.6 mm Hg in the MRA arm and 12.3 mm Hg in the placebo arm, with a between-treatment difference of 2.8 mm Hg.[26] Meanwhile, for patients with baseline SBP greater than 135 mm Hg, SBP decreased by 11.9 mm Hg in the MRA arm and decreased by 10.0 mm Hg in the placebo arm, for a mean treatment difference of 1.8 mm Hg; at 6 months, SBP decreased by 13.0 mm Hg in the MRA arm and decreased by 9.3 mm Hg in the placebo arm, for a mean treatment difference of 3.6 mm Hg.[26] Moreover, ATHENA-HF showed no significant difference in the BP or HR change with higher spironolactone dosing than targeted for HFrEF compared with placebo.[27]

RAASi has a greater effect on BP than SGLT2i and MRA. If patients are hypotensive, this drug class can be started at a later time as hemodynamics allow. A distinction should be made between hypotension and low blood pressure due to high SVR. In situations with high SVR, RAASi may be beneficial for afterload reduction despite a low BP. Of note, despite anecdotal experience possibly suggesting the contrary, the blood pressure effect of sacubitril–valsartan is not more potent than that of an ACEI or an ARB. PIONEER-HF showed that in patients with low versus high SBP, there was no difference in symptomatic hypotension with the inpatient initiation of sacubitril/valsartan compared with enalapril.[28]

With regard to choice of BB, historically, carvedilol has been considered to have greater immediate suppressive effect on blood pressure than metoprolol or bisoprolol due to its additional component of alpha-adrenergic receptor antagonism.[29,30] In one trial, carvedilol depressed BP to a greater degree than metoprolol.[31] In COPERNICUS, among patients with a baseline SBP of 85 to 95 mm Hg, the use of carvedilol (from 3.125 mg BID up-titrated as tolerated to 25 mg BID) did not depress BP compared with placebo.[32] In patients who have HR greater than 70 but who cannot tolerate BB, ivabradine can be considered, as ivabradine reduces HR without depressing BP.[5]

In all patients in whom low blood pressure is a challenge to GDMT use, a review should be undertaken to see if alpha blockers, calcium channel blockers, nitrates, PDE-5 inhibitors can be down-titrated or switched to alternative medications for

Table 2
Overview of guideline-directed medical therapy agents by class, target doses, adverse effects, and number needed to treat for improving all-cause mortality

GDMT Class	Study (Year)	Study Design	Size	Key Outcome
RAASi	CONSENSUS (1987)	Randomized patients with severe HFrEF and New York Heart Association (NYHA) class IV symptoms to enalapril vs standard of care	253	Enalapril improved survival in NYHA class IV HFrEF when added to standard therapy.
	PIONEER-HF (2018)	Randomized patients hospitalized with acute decompensated HFrEF to initiation of sacubitril–valsartan vs enalapril	881	Sacubitril–valsartan reduced NT-proBNP compared with enalapril at 4 and 8 wk without significantly different rates of medication-related adverse effects
	LIFE (2021)	Randomized patients with advanced HFrEF (NYHA class IV) to sacubitril/valsartan vs valsartan	335	There was no significant difference between sacubitril/valsartan vs valsartan in reducing NT-proBNP. There was an increase in non-life-threatening hyperkalemia in the sacubitril/valsartan arm. Otherwise, there were no significant observed safety concerns.
BB	COPERNICUS (2002)	Randomized patients with HFrEF <25% and NYHA class III–IV symptoms to carvedilol vs placebo	2289	Carvedilol reduces the risk of death or HF hospitalization by 31% compared with placebo
	IMPACT HF (2004)	Randomized stabilized patients hospitalized for heart failure to carvedilol initiation pre-discharge vs post-discharge initiation (> 2 weeks)	363	Initiation of BB with carvedilol pre-discharge was associated with increased beta blocker use at 60-d follow-up, compared with initiation of BB therapy after discharge at the discretion of the physician
MRA	EPHESUS (2003)	Randomized patients with acute myocardial infarction (MI) complicated by left ventricle (LV) dysfunction and HF symptoms to eplerenone vs placebo	6642	Eplerenone reduced mortality among patients with acute MI complicated by LV dysfunction and HF symptoms
SGLT-2	SOLOIST-WHF (2021)	Randomized patients with type II diabetes mellitus (DM-2) who were recently hospitalized for worsening heart failure to sotagliflozin vs placebo	1222	Sotagliflozin, initiated before or shortly after discharge, was associated with significantly lower cardiovascular mortality and HF hospitalizations or urgent care visits for HF compared with placebo
	EMPULSE (2022)	Randomized patients with acute decompensated HF (regardless of left ventricular ejection fraction [LVEF]) to empagliflozin vs placebo	530	Initiation of empagliflozin was associated with significant clinical benefit at 90 d in patients hospitalized for acute HF. Clinical benefits are defined as a hierarchical composite of death from any cause, number of HF events, and time to first HF event, or $\geq$ 5 points difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ)
ACEi/ARB/ ARNi, BB and MRA	STONG-HF (2022)	Randomized admitted patients with acute HF who are not on full doses of GDMT to high-intensity up-titration vs usual care	1078	Rapid up-titration of GDMT with close follow-up was safe and associated with reduced risk of 180-d all-cause mortality or HF readmission compared with the usual care

their respective indications. Blood pressure-affecting medications can be retimed and staggered from each other. It is important to treat the patient, not the blood pressure, as it is possible for HFrEF patients to tolerate GDMT despite low BP measurements. It is not uncommon for BP to transiently decrease, especially in the first 2 to 4 hours after administration of a GDMT agent, but medium- and long-term BP changes seem to remain stable. If a patient is free of hypotensive symptoms, such as lightheadedness, GDMT can be continued even if SBP is between 80 and 100 mm Hg.[33]

Heart Failure with Reduced Ejection Fraction with Chronic Kidney Disease

Patients with chronic kidney disease (CKD) are prone to hemodynamic AKI and hyperkalemia, which are common barriers to GDMT initiation/up-titration, but they also represent the subgroup that reaps the most benefit from GDMT.[34] Randomized control trials largely excluded patients with HFrEF advanced CKD, but evidence from recent years have offered reassurance. SGLT2i are renoprotective agents that should be initiated early if the eGFR is $\geq$ 20 mL/min/1.73 m^2. DAPA-CKD[35] and SCORED[36] had enrolled CKD patients with eGFR $\geq$25 mL/min/1.73 m^2, whereas EMPA-KIDNEY, EMPEROR-Reduced,[37] and EMPEROR-Preserved[38] enrolled participants with eGFR $\geq$20 mL/min/1.73 m^2. In DAPA-CKD, dapagliflozin was continued even when eGFR declined to less than 15 mL/min per 1.73 m^2.[39] The Kidney Disease Improving Global Outcomes (KDIGO) 2022 guidelines advocate for the use of SGLT2i even if eGFR reaches less than 20 mL/min/1.73 m^2, until renal replacement therapy is started.[40]

BBs can be initiated and continued during CKD at any time. Observational study from the Swedish Heart Failure Registry showed that BB improved survival in this patient population. Further, BB use decreases cardiovascular mortality and HF hospitalization in CKD patients, with a better outcome in patients with eGFR less than 15 mL/min/1.73 m^2 than in those with an eGFR between 15 and less than 30 mL/min/1.73 m^2.[41]

RAASi should be started if the patients' eGFR is greater than 30 mL/min/1.73 m^2 and potassium is less than 5.0 mmol/L.[42] Specialist supervision and laboratory monitoring in a week after RAASi initiation are warranted in patients with stage 4 or higher CKD. RAASi should not be routinely discontinued even if the eGFR falls below 30 mL/min/1.73 m^2 given the survival benefit with the use of RAASi in CKD patients.[43]

In contrast to the other GDMT agents, MRA is less flexible in CKD. MRA is permitted for eGFR of $\geq$30 mL/min/1.73 m^2 as long as potassium is $\leq$ 5.0 mEq/L, which means that most patients with CKD 4, 5, and end stage kidney disease (ESKD) will not be expected to be on an MRA. Finerenone, non-steroidal MRA has been shown to confer renoprotection in patients with diabetic kidney disease; however, non-steroidal MRA have not been shown to be able to effectively replace steroidal MRA (eg, spironolactone) for the treatment of HFrEF.[40]

Heart Failure with Reduced Ejection Fraction with Worsening Renal Function

WRF after initiation of GDMT should be evaluated in the context of the overall clinical picture. Clinical reasoning is of paramount importance to avoid reflexive discontinuation of GDMT in the name of "acute kidney injury" and the labeling of RAASi as "nephrotoxins."[44] Increasing serum creatinine for patients with HFrEF in the setting of aggressive diuresis and initiation of SGLT2i or RAASi has not only been shown to normalize with time but also confers favorable outcomes in the long term.[45,46] In an analysis of HFrEF patients who received enalapril in SOLVD, enalapril-associated eGFR decline of up to 35% has been associated with reduced HF hospitalization rates; enalapril-associated eGFR decline of up to 15% has been associated improved mortality.[45] Given the protective effect of RAASi for cardiovascular events and mortality, discontinuation of RAASi should be temporary, and to be resumed before discharge.

In EMPA-REG OUTCOME, one-third of the HFrEF patients who were given empagliflozin experienced a decrease in eGFR by greater than 10% within the first 4 weeks. However, eGFR eventually stabilized at week 4, including in patients who had an initial drop in eGFR exceeding 30%.[46] In contrast, patients who were given placebo continued to have a decline in their GFR.[46] Moreover, patients with an eGFR dip did not experience an impact on the treatment effect of empagliflozin on subsequent cardiovascular mortality, HF hospitalization, or incident/worsening kidney disease.

The key is to distinguish between transient WRF on initiation of SGLT2i/RAASi versus AKI or acute tubular injury (ATI). In patients with AKI/ATI, optimization of volume status is imperative to avoid mortality associated with fluid overload. BB can be continued throughout AKI. The same cannot be said for MRA. Given the risk of hyperkalemia with declining renal function, MRA should be deferred until AKI is resolved.

Heart Failure with Reduced Ejection Fraction with Hyperkalemia

Hyperkalemia is common in patients with HFrEF, CKD, and in those receiving RAASi.[47] In these patients, SGLT2i or BB may be most amenable to initiation compared with MRA or RAASi. SGLT2i may enhance kaliuresis through the delivery of sodium to the distal convoluted tubule, activation of tubuloglomerular feedback, activation of RAAS, and secretion of aldosterone, which excrete potassium.[48] Evidence from CREDENCE showed that in CKD patients taking RAASi, canagliflozin actually reduced the risk of hyperkalemia by 23%.[49] BB could be started concurrently with SGT2i in patients with hyperkalemia, as there is no mechanism for BBs to cause hyperkalemia. Post hoc analysis from CAPRICORN and COPERNICUS showed that in CKD patients taking carvedilol, the risk of hyperkalemia was only 2%.[50]

In contrast, RAASi and MRA should be reserved later in GDMT sequencing among patients with hyperkalemia risk. Current HF guidelines advise against MRA use in patients with serum potassium levels greater than 5.0 mEq/L.[42] In regard to RAASi, RESOLVD showed that compared with ACEI, ARB had significantly lower serum potassium, without a change in creatinine level. ELITE similarly showed that in HFrEF patients, the risk of hyperkalemia is higher in ACEIs than ARBs.[51] There was an increase in Ang II with ARB, but the level of aldosterone was similar to that of ACEi.[52]

Acute hyperkalemia during hospitalization should be managed with conventional treatments which include insulin, beta-agonist, diuretics, and potassium binders. In chronic hyperkalemia, the management strategies vary according to region and provider preference. Potassium binders include sodium polystyrene sulfonate, sodium zirconium cyclosilicate (SZC), and patiromer. For patients with and without CKD, SZC significantly reduced potassium levels more than placebo.[53] As SZC works as a sodium/potassium exchanger in the gut, there is concern for volume overload.[54] However, adverse volume effects of SZC including hypertension, weight gain, and edema during hyperkalemia treatment have not been observed. OPAL-HK, which enrolled patients with stages 3 or 4 CKD and serum potassium of 5.1 to 6.5 mEq/L, showed that patiromer was associated with a significant reduction in serum potassium levels (-1.01 ± 0.03 mEq/L) and less recurrence of hyperkalemia.[55] PEARL-HF enrolled 107 HF patients and found that over 90% of the patients receiving patiromer were able to reach the target dose of spironolactone.[56] In DIAMOND, which studied HFrEF patients with eGFR $\geq$30 mL/min/1.73 m^2, compared with placebo, the patiromer treatment group experienced lower incident hyperkalemia and was more likely to continue MRAs than the placebo group; 95% of patients in the treatment group achieved target dose MRA.[57] The number-needed-to-treat (NNT) with patiromer for HFrEF patients with a history of hyperkalemia to avoid one MRA preventable cardiovascular death or hospitalization over 3 years is more than 400.[58] Future studies would need to evaluate the cost-effective and long-term safety of potassium binders in chronic hyperkalemia.

The concept of prioritizing GDMT enabling therapies recognizes that certain medications allow for a higher permissibility or tolerance of side effects from subsequent GDMT classes.[19] For example, post hoc analysis of the PARADIGM-HF (**Fig. 1**) trial showed that compared with enalapril, sacubitril–valsartan was associated with a reduced risk of hyperkalemia in patients receiving MRAs and fewer discontinuations of MRAs.[59] Data from EMPEROR-Pooled (both the EMPEROR-Reduced and EMPEROR-Preserved combined) showed that empagliflozin reduced hyperkalaemia and new initiation of potassium binders; the effect is greater among patients with lower eGFR and among those with a recent HF hospitalization.[60]

Heart Failure with Reduced Ejection Fraction with Atrial Fibrillation

The management of patients with HFrEF and atrial fibrillation (AF) should prioritize optimization of GDMT over the decision of choosing rate versus rhythm control.[61] With regard to choice of AV nodal blockade, BB is preferred over non-dihydropyridine calcium channel blocker (DHP CCB), because CCB is not a component of HFrEF GDMT, and non-DHP CCBs are harmful in HFrEF due to their negative inotropic effects.[5] Similarly, sotalol, flecainide, disopyramide, and dronedarone are contraindicated in HFrEF.[5] The control of AF can improve control of HFrEF and vice versa. Hypervolemic patients with AF should undergo aggressive diuresis, as decongestion would counter the sympathetic drive, slow down the ventricular rate, and increase the success of conversion to sinus rhythm.

Although BBs would ideally be the first agent in this setting ahead of RAASi or MRA, lenient rate control is preferred for HFrEF patients with comorbid AF. Although resting heart rate is associated with cardiovascular mortality and HF hospitalization in HFrEF patients in sinus rhythm, the relationship does not hold true in HFrEF patients with AF.[62] Although guidelines recommend that HFrEF patients in sinus rhythm maintain a resting heart rate

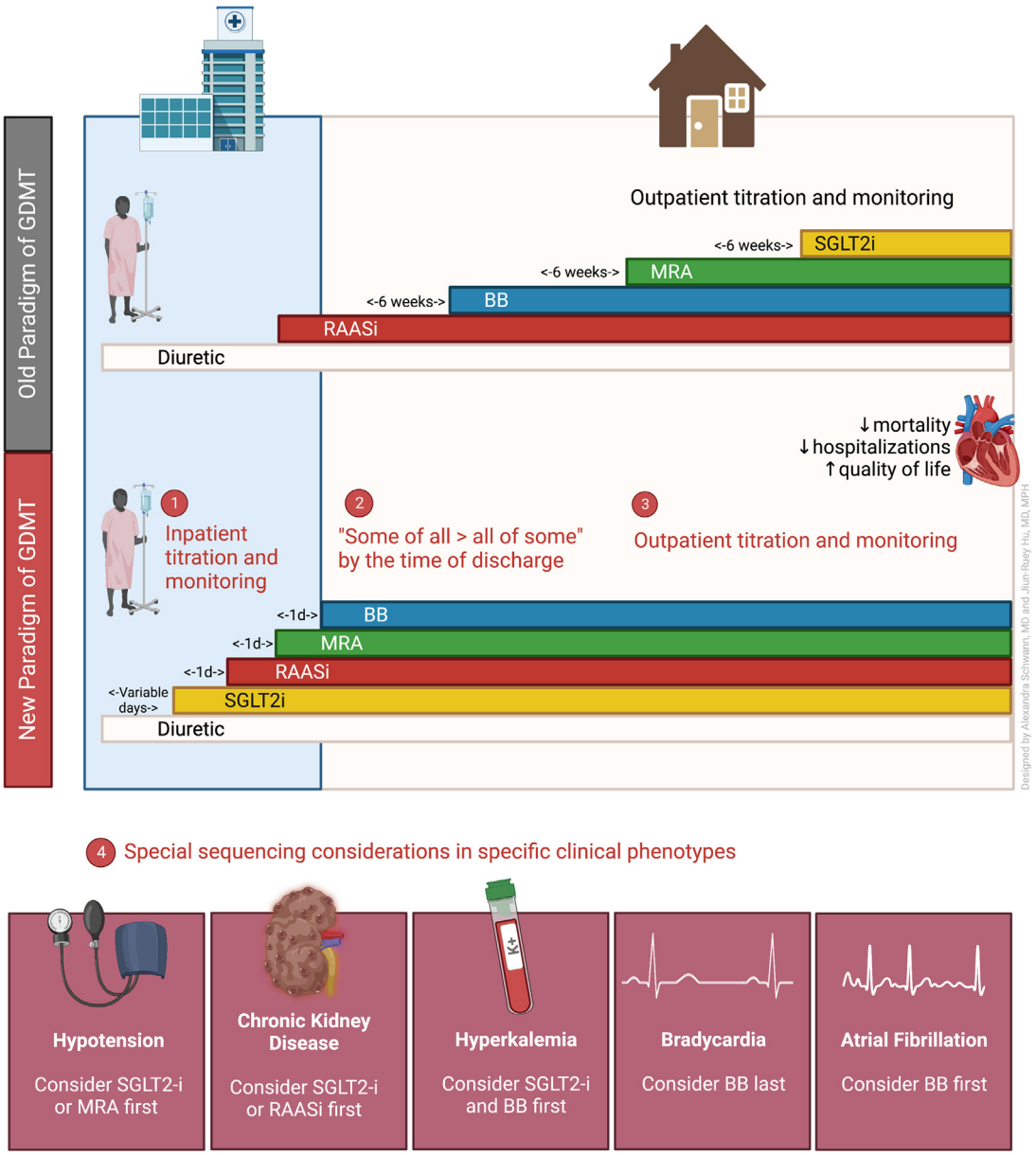

Fig. 1. Figure displaying the contrast of the old vs. new paradigms of GDMT initiation with special sequencing considerations in specific clinical phenotypes. (Created with BioRender.com.)

in the 60s,[5] there is no agreement for the optimal target heart rate for HFrEF patients with AF.[63] The guideline recommendation for using ivabradine to achieve HR less than 70 (Class IIa) only applies to HFrEF patients in sinus rhythm (SR), not HFrEF patients with AF.[5] Patient-level meta-analyses of trials with BB versus placebo in HFrEF found that BB led to a reduction in all-cause mortality and cardiovascular mortality in patients in sinus rhythm, but not in patients with AF.[64,65]

In HFrEF patients with symptomatic AF, ablation is reasonable for improving symptoms and quality of life (Class IIa), as AATAC and CASTLE AF showed a reduction in hospitalization and mortality in HFrEF patients who underwent AF ablation.[66,67] The APAF-CRT mortality trial showed that AV junction ablation plus biventricular pacemaker placement improved survival compared with strict pharmacologic rate control in both patients with HFrEF and patients with HFpEF AV nodal ablation and CRT implantation.[68] Ablation may also pave the way for greater flexibility in deploying HFrEF medications.

Heart Failure with Reduced Ejection Fraction with Bradycardia

For management of HF patients with bradycardia, BB should be sequenced after RAASi, SGLT2i, and MRA, none of which significantly impact heart rate. A medication review should include the consideration of de-prescribing nonessential drugs that have a negative chronotropic effect, such as non-DHP CCBs. If heart rate is less than 50 bpm, BB and ivabradine should be reduced or held. Pacemaker implantation can be considered to allow for up-titration of GDMT,[5] and so as not to lose the adrenergic antagonism benefits of BB. The GDMT class whose mortality benefit is most dose-dependent is BB, although there is value in up-titrating all classes of GDMT, the most value arises from up-titrating BB.[69] With regard to choice of BB, bisoprolol has the greatest immediate suppressive effect on heart rate, followed by metoprolol, then carvedilol,[29,30,70,71] suggesting that if hypertension is present with isolated bradycardia, carvedilol can be considered the evidence-based BB of choice. However, in the long term, there may be no difference in heart rate lowering among individual BB selections. In COMET, a randomized comparison of metoprolol tartrate and carvedilol found a miniscule difference in heart rate at 4 months (<2 bpm) with no difference at 16 months.

SUMMARY

GDMT works. Does the sequence in which GDMT matter? Yes—if it increases the permissibility of initiating the remaining GDMT agents; No—in most other cases, as long as all recommended classes of therapy are eventually prescribed. What matters most is that all patients with HFrEF should be treated with four pillars of GDMT as soon as possible; furthermore, clinicians should endeavor to rapidly titrate these therapies to target or maximally tolerated dosing at the earliest possible occasion. Along with an overview of the safety, efficacy, and tolerability of GDMT, we have carefully discussed several clinical scenarios in which the sequence of GDMT implementation is especially relevant. At times, insightful clinical acumen is necessary for the successful initiation and titration of these medication classes to ensure optimal outcomes for patients with HFrEF. The acute care setting affords a unique, closely monitored environment with emerging evidence to support the safety and effectiveness of intensive GDMT management in stabilized AHF patients. As long as GDMT is initiated appropriately, it is quite safe and well tolerated—even among patients hospitalized with HFrEF. Developing strategies to overcome therapeutic inertia and to achieve maximally tolerated doses of GDMT should be a common goal of all clinicians caring for patients with HFrEF, as GDMT enables patients with HFrEF to live longer, healthier, and higher quality lives.

Abbreviations of Trials

- AATAC: Ablation versus Amiodarone for Treatment of persistent Atrial fibrillation in patients with Congestive heart failure and an implanted device
- APAF-CRT: Atrioventricular Junction Ablation and Biventricular Pacing for Atrial Fibrillation and Heart Failure
- ATHENA-HF: Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure
- CAPRICORN: CArvedilol Post-infaRct survIval COntRolled evaluatioN
- CASTLE-AF: Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation
- CHAMP-HF: Change the Management of Patients with Heart Failure
- COACH-HF: Comparison of Outcomes and Access to Care for Heart Failure Trial
- COMET: Carvedilol Or Metoprolol European Trial
- COPERNICUS: Carvedilol Prospective Randomized Cumulative Survival
- CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
- DAPA-CKD: Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
- DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
- DIAMOND: Patiromer for the Management of Hyperkalemia in Subjects Receiving RAASi Medications for the Treatment of Heart Failure
- EMPA-KIDNEY: The Study of Heart and Kidney Protection With Empagliflozin
- EMPA-REG OUTCOME: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
- EMPA-RESPONSE-AHF: Randomized, Double-Blind, Placebo-Controlled, Multicenter Pilot Study on the Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure
- EMPEROR-Reduced: EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction
- EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction

- EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
- EMPULSE: EMPagliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalised for acUte Heart faiLure (de Novo or Decompensated Chronic HF) Who Have Been StabilisEd
- ELITE: Evaluation of Losartan in the Elderly Study
- IMPACT-HF: Initiation Management Predischarge Process for Assessment of Carvedilol Therapy for Heart Failure
- OPAL-HK: A Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia
- PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure
- PEARL-HF: Multicenter, Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multiple-Dose to Evaluate the Effects of RLY5016 in Heart Failure Patients
- PIONEER-HF: Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode
- Potassium Reduction Initiative to Optimize RAAS Inhibition Therapy With Sodium Zirconium Cyclosilicate in Heart Failure
- RALES: Randomized Aldactone Evaluation Study
- SCORED: Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk
- SOLVD: Studies of Left Ventricular Dysfunction
- STRONG-HF: Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure

CLINICS CARE POINTS

- Guideline directed medical therapy is a life saving intervention for patients with heart failure with reduced ejection fraction. It is imperative that patients with this disease be provided with these disease modifying therapies.
- The order by which forms of guideline directed medical therapy are initiated matters less than the end result whereby patients with heart failure with reduced ejection fraction have been started on all four pillars of therapy.
- Special sequencing considerations in specific clinical phenotypes can allow for the ultimate goal of achieving initiation of all four pillars of guideline directed medical therapy in patients with heart failure with reduced ejection fraction.

DISCLOSURE

No grants, contracts, or other forms of financial support were received for this article. Dr Ralph Riello is on the advisory board of AstraZeneca, Janssen and Johnson & Johnson and has received honoraria/consultation fees from Janssen, Johnson & Johnson, and Pfizer. All remaining authors have no disclosures.

REFERENCES

1. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet 2019; 393(10166):61–73.
2. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American heart association joint Committee on clinical practice guidelines. J Am Coll Cardiol 2022;79(17):e263–421.
3. Tan J, Hu JR. GDMT for Everyone. Guideline-Directed Medical Therapy for Everyone. Published May 2022. Available at: www.GDMT.org. Accessed January 31, 2023.
4. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet 2022. https://doi.org/10.1016/S0140-6736(22)02076-1.
5. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American heart association joint Committee on clinical practice guidelines. Circulation 2022;145(18):e895–1032.
6. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin–neprilysin inhibition in acute decompensated heart failure. N Engl J Med 2019;380(6):539–48.
7. Gattis WA, O'Connor CM, Gallup DS, et al. IMPACT-HF Investigators and Coordinators. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the initiation management Predischarge: process for assessment of carvedilol therapy in heart failure (IMPACT-HF) trial. J Am Coll Cardiol 2004;43(9):1534–41.
8. Ko DT, Hebert PR, Coffey CS, et al. Adverse effects of β-blocker therapy for patients with heart failure: a

quantitative overview of randomized trials. Arch Intern Med 2004;164(13):1389–94.
9. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. J Am Coll Cardiol 2018;72(4):351–66.
10. Eschalier R, McMurray JJV, Swedberg K, et al. Safety and efficacy of Eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild patients hospitalization and SurvIval study in heart failure). J Am Coll Cardiol 2013;62(17):1585–93.
11. Maisel A, Xue Y, van Veldhuisen DJ, et al. Effect of spironolactone on 30-day death and heart failure rehospitalization (from the COACH study). Am J Cardiol 2014;114(5):737–42.
12. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. JAMA Cardiol 2017;2(9):950–8.
13. Butler J, Anker SD, Lund LH, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. Eur Heart J 2022;43(41):4362–73.
14. Buysse JM, Huang IZ, Pitt B. PEARL-HF: prevention of hyperkalemia in patients with heart failure using a novel polymeric potassium binder, RLY5016. Future Cardiol 2012;8(1):17–28.
15. Vukadinović D, Lavall D, Vukadinović AN, et al. True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: a meta-analysis. Am Heart J 2017;188:99–108.
16. Struthers A, Krum H, Williams GH. A comparison of the aldosterone-blocking agents Eplerenone and spironolactone. Clin Cardiol 2008;31(4):153–8.
17. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med 2022;28(3):568–74.
18. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet Lond Engl 2020;396(10254):819–29.
19. Greene SJ, Butler J, Metra M. Another reason to embrace quadruple medical therapy for heart failure: medications enabling tolerance of each other. Eur J Heart Fail 2021;23(9):1525–8.
20. Lega IC, Bronskill SE, Campitelli MA, et al. Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: a population-based study of older women and men with diabetes. Diabetes Obes Metab 2019;21(11):2394–404.
21. McMurray JJV, Packer M. How should we sequence the treatments for heart failure and a reduced ejection fraction? Circulation 2021;143(9):875–7.
22. Bozkurt B. How to initiate and uptitrate GDMT in heart failure: practical stepwise approach to optimization of GDMT. JACC Heart Fail 2022;10(12):992–5.
23. Greene SJ, Butler J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure—optimizing therapy with the need for speed. JAMA Cardiol 2021;6(7):743–4.
24. Griffin M, Rao VS, Ivey-Miranda J, et al. Empagliflozin in heart failure. Circulation 2020;142(11):1028–39.
25. Serenelli M, Böhm M, Inzucchi SE, et al. Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). Eur Heart J 2020;41(36):3402–18.
26. Serenelli M, Jackson A, Dewan P, et al. Mineralocorticoid receptor antagonists, blood pressure, and outcomes in heart failure with reduced ejection fraction. Jacc Heart Fail 2020;8(3):188–98.
27. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute heart failure. JAMA Cardiol 2017;2(9):950–8.
28. Berg DD, Samsky MD, Velazquez EJ, et al. Efficacy and safety of sacubitril/valsartan in high-risk patients in the PIONEER-HF trial. Circ Heart Fail 2021;14(2):e007034.
29. Stoschitzky K, Stoschitzky G, Brussee H, et al. Comparing beta-blocking effects of bisoprolol, carvedilol and nebivolol. Cardiology 2006;106(4):199–206.
30. Stoschitzky K, Koshucharova G, Zweiker R, et al. Differing beta-blocking effects of carvedilol and metoprolol. Eur J Heart Fail 2001;3(3):343–9.
31. Sanderson JE, Chan SK, Yip G, et al. Beta-blockade in heart failure: a comparison of carvedilol with metoprolol. J Am Coll Cardiol 1999;34(5):1522–8.
32. Rouleau JL, Roecker EB, Tendera M, et al. Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study. J Am Coll Cardiol 2004;43(8):1423–9.
33. Bozkurt B. Response to Ryan and Parwani: heart failure patients with low blood pressure: How should we manage neurohormonal blocking drugs? Circ Heart Fail 2012;5(6):820–1.
34. Vaduganathan M, Fonarow GC, Greene SJ, et al. Treatment persistence of renin-angiotensin-aldosterone-system inhibitors over time in heart failure with reduced ejection fraction. J Card Fail 2022;28(2):191–201.
35. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383(15):1436–46.
36. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384(2):117–28.

37. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383(15):1413–24.
38. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385(16):1451–61.
39. Chertow GM, Vart P, Jongs N, et al. Effects of dapagliflozin in stage 4 chronic kidney disease. J Am Soc Nephrol 2021;32(9):2352–61.
40. Rossing P, Caramori ML, Chan JCN, et al. Executive summary of the KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease: an update based on rapidly emerging new evidence. Kidney Int 2022;102(5):990–9.
41. Fu EL, Uijl A, Dekker FW, et al. Association between β-blocker use and mortality/morbidity in patients with heart failure with reduced, midrange, and preserved ejection fraction and advanced chronic kidney disease. Circ Heart Fail 2020;13(11):e007180.
42. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. J Card Fail 2017;23(8):628–51.
43. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013; Suppl(3):1–150.
44. Bozkurt B. The need to stop Inappropriate Coding for acute kidney injury in heart failure. JACC Heart Fail 2022;10(9):692–4.
45. McCallum W, Tighiouart H, Ku E, et al. Acute declines in estimated glomerular filtration rate on enalapril and mortality and cardiovascular outcomes in patients with heart failure with reduced ejection fraction. Kidney Int 2019;96(5):1185–94.
46. Kraus BJ, Weir MR, Bakris GL, et al. Characterization and implications of the initial estimated glomerular filtration rate 'dip' upon sodium-glucose cotransporter-2 inhibition with empagliflozin in the EMPA-REG OUTCOME trial. Kidney Int 2021;99(3):750–62.
47. Jain N, Kotla S, Little BB, et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. Am J Cardiol 2012;109(10):1510–3.
48. Heerspink HJL, Perkins BA, Fitchett DH, et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus. Circulation 2016; 134(10):752–72.
49. Neuen BL, Oshima M, Perkovic V, et al. Effects of canagliflozin on serum potassium in people with diabetes and chronic kidney disease: the CREDENCE trial. Eur Heart J 2021;42(48):4891–901.
50. Wali RK, Iyengar M, Beck GJ, et al. Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease. Circ Heart Fail 2011;4(1): 18–26.
51. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997;349(9054):747–52.
52. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of Candesartan, enalapril, and their Combination in Congestive heart failure. Circulation 1999;100(10): 1056–64.
53. Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med 2015;372(3):222–31.
54. Lokelma® (sodium zirconium cyclosilicate) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2022.
55. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med 2015; 372(3):211–21.
56. Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J 2011;32(7):820–8.
57. Tromp J, Ouwerkerk W, van Veldhuisen DJ, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. JACC Heart Fail 2022; 10(2):73–84.
58. Packer M. Potassium binders for patients with heart failure? The real enlightenment of the DIAMOND trial. Eur Heart J 2022;43(41):4374–7.
59. Desai AS, Vardeny O, Claggett B, et al. Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: a secondary analysis of the PARADIGM-HF trial. JAMA Cardiol 2017;2(1):79–85.
60. Ferreira JP, Zannad F, Butler J, et al. Empagliflozin and serum potassium in heart failure: an analysis from EMPEROR-Pooled. Eur Heart J 2022;43(31): 2984–93.
61. Lee JZ, Cha YM. Atrial fibrillation and heart failure: a contemporary review of current management approaches. Heart Rhythm O2 2021;2(6):762–70. Part B).
62. Docherty KF, Shen L, Castagno D, et al. Relationship between heart rate and outcomes in patients in sinus rhythm or atrial fibrillation with heart failure and reduced ejection fraction. Eur J Heart Fail 2020; 22(3):528–38.
63. Bauersachs J, Veltmann C. Heart rate control in heart failure with reduced ejection fraction: the bright and the dark side of the moon. Eur J Heart Fail 2020;22(3):539–42.
64. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range,

and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J 2018;39(1):26–35.
65. Kotecha D, Holmes J, Krum H, et al. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet 2014;384(9961):2235–43.
66. Di Biase L, Mohanty P, Mohanty S, et al. Ablation versus Amiodarone for treatment of persistent atrial fibrillation in patients with Congestive heart failure and an implanted device. Circulation 2016;133(17):1637–44.
67. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378(5):417–27.
68. Brignole M, Pentimalli F, Palmisano P, et al. AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial. Eur Heart J 2021;42(46):4731–9.
69. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in Left ventricular function and survival in Subjects with chronic heart failure. Circulation 1996;94(11):2807–16.
70. Stoschitzky K, Donnerer J, Klein W, et al. Different effects of propranolol, bisoprolol, carvedilol and doxazosin on heart rate, blood pressure, and plasma concentrations of epinephrine and norepinephrine. J Clin Basic Cardiol 2003;6(1):69–72.
71. Vittorio TJ, Zolty R, Kasper ME, et al. Differential effects of carvedilol and metoprolol succinate on plasma norepinephrine release and peak exercise heart rate in Subjects with chronic heart failure. J Cardiovasc Pharmacol Ther 2008;13(1):51–7.